REMARKS

Claims 1, 2, 5-10 and 20 presently appear in this case. No claims have been allowed. The official action of January 25, 2008, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for the treatment of accelerated bone resorption that is not induced by inflammation in a mammal subject. This is accomplished by administering to the subject an amount of A_3 adenosine receptor agonist (A_3AR agonist), in an amount effective to inhibit bone resorption.

Claims 1-6, 9 and 10 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Fishman. The examiner states that Fishman discloses a method of treating inflammatory arthritis comprising administering to a subject an A_3AR agonist, specifically IB-MECA and Cl-IB-MECA. The examiner states that Fishman reduces the bone loss in the subject by administering IB-MECA and reports that bone loss was markedly lower in the subjects treated with IB-MECA. The examiner states that it would have been obvious in view of Fishman to treat bone resorption, whether it is accelerated or not, by administering an A_3AR agonist, since Fishman teaches that such can be used to treat bone resorption. This rejection is respectfully traversed.

Fishman is directed to the use of IB-MECA or Cl-IB-MECA for the treatment of inflammatory arthritis. At page 3, lines 21 and 22, Fishman states that in some patients with rheumatoid arthritis, chronic inflammation leads to the destruction of the cartilage, bone and ligaments causing deformity of the joints. It can be seen from the paragraph beginning at page 4, line 11, that the disease-modifying effect of IB-MECA or Cl-IB-MECA is termed "anti-inflammatory" as it alleviates the inflammatory response in inflammatory arthritis. The anti-inflammatory response may be determined on the basis of various histological parameters. As seen in the paragraph beginning at page 7, line 10, the treatment of inflammatory arthritis includes an improvement manifested by any of the number of parameters including slowing of the deterioration of the joints. In Example 1C, for example, one of the parameters added into the histology score was a bone damage and erosion score. It is noted that the Fishman patent publication does not specify any particular histology score particularly for the bone damage so it is not clear from this publication what that particular score was in Example 1C.

The examiner states that Fishman measures the loss of bone and reports that bone loss was markedly lower in the subjects treated with IB-MECA, citing the reference to the histology score in example 1C. However, applicant fails to see

where this comment of the examiner is supported in Example 1C. The histology score merely explains what the score of 1-5 means when measuring bone damage and erosion. It can be seen from example 1C that parameters (a), (b), (c), and (d) were measured using a grading scale of 0-4 and (e) was evaluated using a grading scale of 1-5 as defined therein. However, the only reference to the results of the histology score relates to the mean of all of the histological parameter scores. This is shown in Fig. 8. That teaches nothing about what was the specific histology score that was measured for parameter (e). Accordingly, it is nowhere disclosed that IB-MECA had a marked effect to bone loss, or any other effect on bone loss.

While it is not clear from a reading of Fishman on its face whether or not IB-MECA or Cl-IB-MECA would actually treat bone resorption, for the reasons discussed above, nevertheless, in order to expedite allowance, the present claims have now been amended to specify that the method is for the treatment of accelerated bone resorption that is not induced by inflammation. The present specification states, in the paragraph bridging pages 4 and 5, that accelerated bone resorption refers to a disease, disorder or pathological condition that may result from accelerated metabolic processes induced by inflammation or by any other pathological condition. See also page 16 in the paragraph beginning at line 22, where it states that accelerated

bone loss may be due to an accelerated metabolic process as a result of a bone disease or it may be induced by inflammation. Accordingly, it is clear from the present specification that A_3AR agonists may be used to treat accelerated bone loss whether induced by inflammation or which is a result of some other pathological condition. As stated in MPEP 2173.05(i):

> If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.

Those of ordinary skill in the art reading the Fishman reference, if taught anything at all about the effect of IB-MECA or Cl-IB-MECA on bone resorption when treating inflammatory arthritis patients, would only be taught that this is a side effect of the anti-inflammatory treatment. There certainly would be no suggestion that IB-MECA or Cl-IB-MECA, or any other A_3AR agonist, would be operable to treat accelerated bone resorption in diseases or conditions that are not related to inflammation.

Accordingly, as there is nothing in Fishman that explicitly teaches that IB-MECA or Cl-IB-MECA will cause a marked reduction in bone loss, as there is nothing in Fishman that would suggest that any effect of IB-MECA or Cl-IB-MECA on bone loss is due to anything other than its anti-inflammatory effect, and as the present claims have now been amended so as to exclude treatment of accelerated bone loss induced by

inflammation, the present claims are neither anticipated nor made obvious by Fishman. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

While it is not believed that this information is necessary in order to establish patentability of the present claims over Fishman, for the examiner's information, attached hereto is a summary of data from experiments that were performed by the present applicants. This data shows that bone loss takes place as a result of osteoclast differentiation (osteoclasts are cells that are responsible for bone destruction and the formation of bone loss) and that CF101 (A_3AR agonist) inhibits osteoclast formation by a down regulation of RANKL, thus preventing bone loss. Surprisingly, the effect of A_3AR on preventing bone resorption is based on a fact independent of its anti-inflammatory effect. This would certainly have not been obvious to anyone of ordinary skill in the art reading the Fishman reference. If the examiner believes it would be useful, applicant can submit this data in the form of a declaration.

An error has now been identified in the present specification and claims. In the present specification at page 15 and in present claim 8, the designation R_4 should obviously be R_5. In the formula (I) of claim 7, as well as formula (I) of claim 13, R_3 is defined as a group of the formula $-NR_4R_5$. The formula (IV) shows R_3 being "NHR_4." This, of course, is

impossible as in the definition of R_4 and R_5, only R_4 can be a hydrogen atom. As one of the two moieties attached to the nitrogen atom in formula (IV) is a hydrogen atom, the other one must be R_5, not R_4. This was a clerical error, but for the above reasons it is believed to be an obvious error and the correction is also obvious. Accordingly, the specification and claim 8 have now been amended to change R_4 to R_5 in formula (IV). Thus, the compounds of Formula (IV) are properly made to correspond to a preferred embodiment of the compounds of Formula (I).

It should be noted that, contrary to the examiner's statement, the formulas of both claims 7 and 8 (after the present amendment) read on both IB-MECA and Cl-IB-MECA.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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Effect of CF101 on bone resorption

Bone resorption is the process by which osteoclasts, bone resorbing and remodeling cells, break down bone and release the minerals, resulting in a transfer of calcium from bone fluid to the blood. Osteoclasts formation and activity is increased in inflammatory diseases, inflammatory osteolysis and skeletal tumor metastases resulting in extreme bone loss (1).

The osteoclasts are multi-nucleated hematopoietic cells which are formed by the fusion of precursors derived from the monocyte/macrophage lineage. Osteoclasts formation requires the presence of RANK ligand (receptor activator of nuclear factor κβ) and M-CSF (Macrophage colony-stimulating factor). Osteoclasts differentiation is inhibited by osteoprotegerin (OPG), which binds to RANKL thereby preventing interaction with it receptor, RANK. (1,2).

RANKL is a member of the tumor necrosis family (TNF), and is essential in osteoclastogenesis. RANKL activates the NF-κB signaling pathway which is essential for the differentiation and survival of osteoclasts (3). NF-κB is known to play a key role in the pathogenesis of various inflammatory diseases, including Rheumatoid Arthritis and inflammatory bone erosion (4-6). NF-κB induces the expression of pro-inflammatory cytokines and osteocalstogenic factors, such as TNF-α and RANKL (by an autocrine loop), respectively (4, 7, 8).

The mouse macrophage cell line RAW264.7 is known to express RANK and to differentiate into osteoclasts, when incubated with RANKL and are known to be stained by tartrate resistance acid phosphatase (TRAP).

The RAW264.7 cell line was obtained from the American Type Culture Collection and cultured in DMEM medium supplemented with 10% of FBS, 2mM glutamine, 100 U/ml penicillin and 100µg/ml streptomycin in a 37^0C, 5% CO_2 incubator. The cells were cultured on glass cover slides coated with Poly L-Lysin in 2ml Petri dishes, at a density of 1000cells/ml and were allowed to adhere over night. The growth medium was then replaced with a fresh medium and the cells were treated with 50ng/ml of RANKL in the presence or absence of CF101 (10nM). At day 5 the cultures were stained for TRAP expression using an acid phosphatase kit. For each sample 3 counts of TRAP-positive multinucleated osteoclasts (at a plot of $2mm^2$) was performed.

Figure 1. demonstrates the ability of CF101 to inhibit osteoclastogenesis induced by RANKL in RAW 264.7 macrophage cell line.

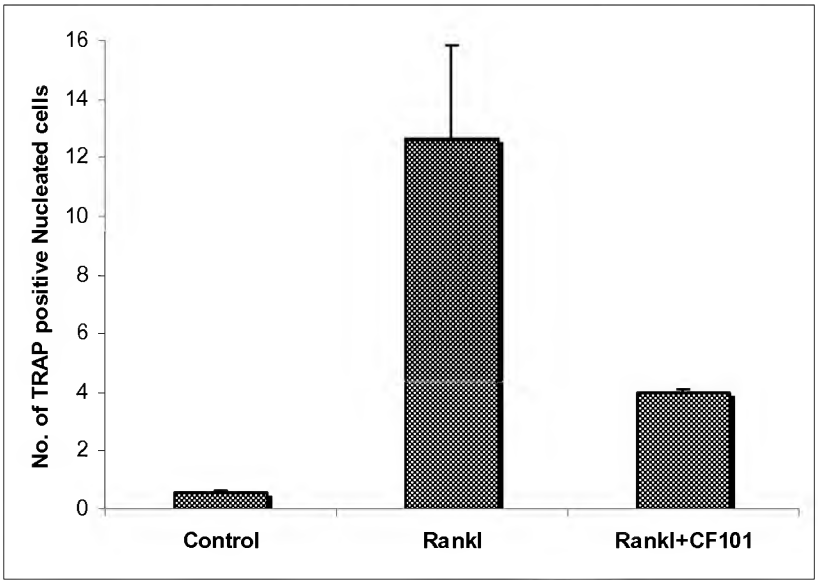

Figure 1.

CF101 treatment inhibited by 68% the number of TRAP positive cells, demonstration the ability of CF101 to inhibit the differentiation of RAW264.7 macrophages to osteoclasts.

Lipopolysaccharide (LPS) is a potent bone resorbing factor. It was found that LPS induced the formation of multinucleated giant cells which were positive for TRAP activity. Therefore, LPS was suggested to induce osteoclast formation in RAW 264.7 cells. Inhibitors of NF-κB prevented the LPS-induced osteoclast formation. (9).

In light of the above the ability of CF101 to down-regulate the expression level of NF-κB in LPS activated RAW 264.7 cells was tested. The cells were incubated with LPS (10ng/ml) for 48 hours. At the last 24 hours of the culture CF101 (10nM) was added. The cells were collected and subjected for western blot analysis to evaluate the expression level of the NF-κB.

Figure 2. demonstrates that CF101 down-regulated the expression level of NF-κB in LPS activated RAW 264.7 cells.

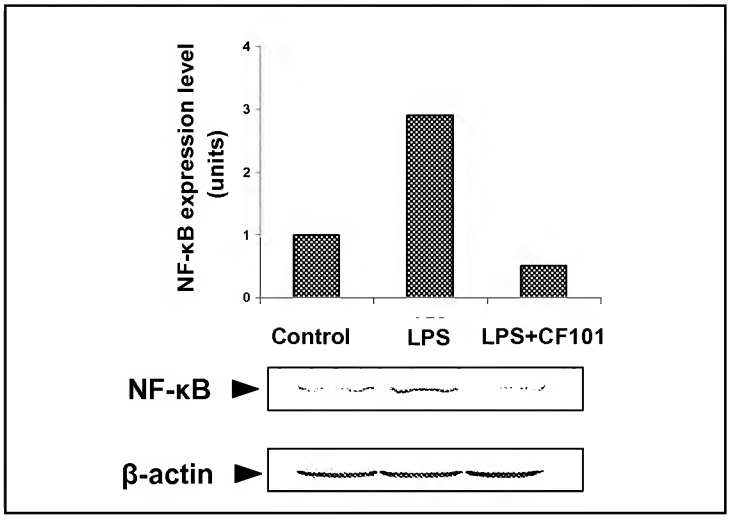

Figure 2.

The expression level of NF-κB was up-regulated in RAW 264.7 cells upon activation with LPS. Administration of CF101 decreased the level of NF-κB, which may lead to the inhibition of the differentiation of the cells to osteoclasts.

To conclude, in this study we showed that CF101 inhibits bone resorption via its ability to prevent osteoclasts formation.

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